Applicants: James Binley et al.
Serial No.: 10/780,993
Filed: January 18, 2004
Exhibit 8

Office Action Summary	Application No.	Applicant(s)	
	10/489,040	MOORE ET AL.	
	Examiner	Art Unit	
	Louise Humphrey, Ph.D.	1648	

– The MAILING DATE of this communication appears on the cover sheet with the correspondence address –

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *27 November 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *112-120,123-125 and 127-134* is/are pending in the application.

4a) Of the above claim(s) *114 and 127-134* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *112,113,115-120 and 123-125* is/are rejected.

7)☒ Claim(s) *112* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

Applicants: James Binley et al.
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DETAILED ACTION

This Office Action is in response to the amendment filed 27 November 2006. Claims 1-111, 121, 122 and 126 have been canceled. Claims 112-120, 123-125, and 127-134 are pending. Claims 114 and 127-134 are withdrawn. Claims 112, 113, 115-120, and 123-125 are under final rejection.

The objection to the specification and the oath/declaration is **withdrawn** in view of the Applicant's amendment and submission of a new oath/declaration.

The objection to claim 122 is **withdrawn** in view of the claim cancellation.

The amended claim 112 is objected to for containing an extra word "and" between the phrases "an amino acid" and " position selected from" in line 13.

Response to Arguments

Claim Rejections - 35 U.S.C. §112

The following is a quotation of the first paragraph of 35 U.S.C. §112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The following is a quotation of the second paragraph of 35 U.S.C. §112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The rejection of claim 112 under 35 U.S.C. §112, second paragraph, as being indefinite is **maintained** because, in the amended claim, it is unclear how many mutations are in the claimed protein? The recitation of "the second modified gp41 polypeptide" implies that there is a first modified gp41 polypeptide, however the context

suggests that the claim is referring to the modified gp41, alternatively referred to as the second polypeptide. Is the phrase "further comprises at least one amino acid" recited in (i) referring to the same mutation as the phrase "the second cysteine introduced by a mutation", or in addition to the second mutation that introduces a second cysteine in the claimed protein? Is the mutation by insertion or substitution?

Claims 113,115-120 and 123-125 are rejected for depending from an indefinite base claim.

The rejection of claims 1112, 113, 115-120, and 123-125 under 35 U.S.C. §112, first paragraph, as failing to comply with the written description requirement is **withdrawn** in view of the amendment adding limitations of specific mutation sites.

Claim Rejections - 35 U.S.C. §102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. §102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.
>
> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting

directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

The rejection of claims 112, 113, 115, 116, 119, and 124 under 35 U.S.C. §102(b) as being anticipated by Binley *et al.* (2000) is **withdrawn** in view of the amendment adding a limitation of mutational sites.

The rejection of claims 112, 113, 115-120, 124 and 125 under 35 U.S.C. §102(e) as being anticipated by Binley *et al.* (US 2003/0052839, now patented as US 7,022,324) is **withdrawn** in view of the amendment adding a limitation of mutational sites. It is noted that Applicants stated the wrong patent number, US 7,022,234, in the response filed on 27 November 2006.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. §103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The rejection of claims 112, 113, 115, 116, 119, 123 and 124 under 35 U.S.C. §103 (a) as being obvious over Binley *et al.* (2000, Jan) in view of Chen *et al.* (1993) is **maintained**.

The instant claims, as amended, are directed to a protein comprising a first polypeptide which comprises consecutive amino acids encoding a modified gp120 of a

HIV-1 isolate, which modified gpl20 includes a first cysteine introduced by a mutation, and a second polypeptide which comprises consecutive amino acids encoding a modified gp41 ectodomain of such HIV-1 isolate, which modified gp41 ectodomain includes a second cysteine introduced by a mutation, wherein (i) the second modified gp41 polypeptide further comprises at least one mutation amino acid in its N-terminal helix, wherein the at least one amino acid is introduced as a result of a mutation and is located at a position which, in the wild type of the second polypeptide, corresponds to an amino acid position selected from the group consisting of V583, V580, L576, I573, T569, L566, Q562, Q590, L587, L555, Q552, I548, L545 and I559, such wild type amino acids and their positions being numbered by reference to the HIV-1 isolate HIV-1_{HXB2}, and (ii) the first and second polypeptides are bound to one another by a disulfide bond between the first cysteine and the second cysteine.

Examiner's rejection in the Action mailed on 19 May 2006 is as follows:

Binley *et al.* teach a recombinant HIV-1 envelope glycoprotein complex stabilized by an intermolecular disulfide bond between the gp120 and gp41 subunits, which mimics the monomeric unit of the trimeric complex of HIV envelope glycoprotein (Title and Abstract). Specifically, Binley *et al.* teach a group of cysteine mutants of HIV subtype B, strain JR-FL, gp140 (p. 628, left column, ¶ 5, right column, last ¶, and Fig. 7), including quadruple cysteine substitutions such that the gp41 ectodomain comprises one more mutation in the N-terminal helix. Binley *et al.* further teach mutated furin recognition sequence by amino acid substitution (p. 628, left column, ¶ 4).

Binley *et al.* do not teach the additional mutation in the second polypeptide at the indicated position.

Chen *et al.* teach substitution of Ile-559 with Pro residue to disrupt the N-terminal helix (p. 3615, right column, ¶3) and disclose that the 1559P mutation does not affect Env protein oligomerization but affect virus infectivity (p. 3618, left column, ¶3, and Table 1).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the HIV-1 gp120 monomer of Binley *et al.* by adding mutation I559P in gp41 such that the infectivity of the peptide is reduced. One having ordinary skill in the art would have been motivated to do this to obtain safety for

these immunogenic peptides without changing the overall structure, so as to maintain the antigenic properties, as suggested by Chen *et al.*

Applicants contend that one skilled in the art would not expect that combining the teachings of Chen *et al.* with those of Binley *et al.* would result in increased stability and oligomerization. Applicants further contend that the claimed protein possesses unexpected properties that the amino acid substitutions in the modified gp41 polypeptide increases both stability and oligomerization of the protein. Applicant's arguments have been fully considered but are not persuasive.

The motivation provided in Chen *et al.* is to reduce viral infectivity without affecting oligomerization (see the last paragraph) so as to preserve the oligomeric conformation of gp120-gp41 complexd and increase the safety of the immunogenic synthetic Env protein. In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (*i.e.*, increased stability and oligomerization) are not recited in the rejected claims. Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

New Rejections Necessitate by the Amendment

Claims 112, 113, 115, 116, 119, 120, and 123-125 are rejected under 35 U.S.C. §103(a) as being unpatentable over Binley *et al.* (2000) in view of Chen *et al.* (1993), and further in view of Barnett *et al.* (US 6,602,705 B1).

The instant invention is further limited to the canonical glycosylation sites and a composition comprising the modified stable HIV-1 trimeric complex.

The relevance of Binley *et al.* and Chen *et al.* is set forth above. Neither reference teaches the change of canonical glycosylation sites absent in HIV-1 gp120 and a composition.

Barnett *et al.* describe antigen-presenting and immune-stimulating compositions that include various excipients, adjuvants, carriers, modulating agents, and the like. Antigens include gp120, gp41, gp160, Gag and Pol from a variety of HIV isolates from diverse subtypes A through G and O. See column 42, lines 13-20. One embodiment of the antigen is the HIV-1_{SF2} Env polypeptide, which can exist in both monomeric and trimeric forms. See column 57, lines 12-45. Barnett *et al.* further suggest ways to manipulate Env coding sequences to maximize gene expression: sequences encoding hypervariable regions of Env, particularly V1 and/or V2 are deleted; N-glycosylation sites are removed and/or cleavage sites are mutated. See column 58, lines 15-27.

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the HIV Env complex of Binley *et al.* and Chen *et al.* by formulating a composition and mutating canonical glycosylation sites, as taught by Barnett *et al.* The skilled artisan would have been motivated to do so to increase the immunogenicity of the HIV Env composition. There would have been a reasonable expectation of success, given that mutating glycosylation sites can maximize gene expression and thereby elicit more immune response to HIV, as taught by Barnett *et al.*

Thus, the invention as a whole was clearly prima facie obvious to one of ordinary skill in the art at the time the invention was made.

Claims 112, 113, 115-120 and 123-125 are rejected under 35 U.S.C. §103(a) as being obvious over Binley *et al.* (US 7,022,324 B2, hereafter referred to as '324 patent) in view of Chen *et al.* (1993).

The applied reference has a common assignee with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. §102(e). This rejection under 35 U.S.C. §103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. §104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). This rejection might also be overcome by showing that the reference is disqualified under 35 U.S.C. §103(c) as prior art in a rejection under 35 U.S.C. §103(a). See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The instant invention is further limited to the glycosylation sites and a disulfide bond between cysteine residues introduced by indicated mutations.

The '324 patent teaches an isolated HIV-1_{JR-FL} envelope glycoprotein complex comprising a gp120 and gp41 bound to one another by a disulfide bond between a cysteine residue introduced by an A492C mutation into gp120 and a cysteine residue introduced by a T596C mutation into gp41 (¶127, ¶129, and ¶130), wherein the gp41 further comprises a mutation at the N-terminal helix, P600C (¶275). The modified gp120 further comprises a mutated furin cleavage site (¶67) and is characterized by the presence of one or more canonical glycoylation sites not present in wild type gp120, or

by the absence of one or more canonical glycosylation sites present in wild type gp120 (¶114-115). The '324 patent further teaches a trimer comprising three identical modified proteins of gp120 bound to gp41, a composition comprising an adjuvant and the HIV envelope complex or the trimer (Claims).

The '324 patent does not teach the additional mutation in the second polypeptide at the indicated position in the amended claim limitation.

Chen *et al.* disclose substitution of Ile-559, Leu-566, Ile-573, or Leu-587 with Pro residue to disrupt the N-terminal helix helix (p. 3615, right column, ¶3) and disclose that the mutation does not affect Env protein oligomerization but affect virus infectivity (p. 3618, left column, ¶3, and Table 1).

It would have been prima facie obvious to a person of ordinary skill in the art at the time the invention was made to modify the HIV Env complex or trimer of '324 patent by adding mutation I559P, L566P, I573P or L587P in gp41 such that the infectivity of the peptide is reduced. One having ordinary skill in the art would have been motivated to do this to obtain safety for these immunogenic peptides without changing the overall structure, so as to maintain the antigenic properties, as suggested by Chen *et al.*

Conclusion

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action

Contact Information

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Louise Humphrey, Ph.D. whose telephone number is 571-272-5543. The examiner can normally be reached on Mon-Fri, 9:30 am - 5:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Bruce Campell, can be reached at 571-272-0974. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Jeffrey Parkin, Ph.D.
Primary Examiner
16 March 2007

Louise Humphrey, Ph.D.
Assistant Examiner

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SHORTENED STATUTORY PERIOD OF RESPONSE	MAIL DATE	DELIVERY MODE
3 MONTHS	03/23/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

If NO period for reply is specified above, the maximum statutory period will apply and will expire 6 MONTHS from the mailing date of this communication.